IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2006_1312A
Hiide YOSHINO et al.	:	**Confirmation No. 4646**
Serial No. 10/588,778	:	Group Art Unit 1628
Filed December 3, 2007	:	Examiner Marcos L. Sznaidman
A NOVEL THERAPEUTIC AGENT FOR AMYOTROPHIC LATERAL SCLEROSIS (ALS) OR DISEASES CAUSED BY ALS	:	**Mail Stop: AF**

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Koji Abe, M.D., Ph.D., the undersigned, a citizen of Japan, (my full post office address is c/o Okayama University Medical School, 2-5-1 Shikata-cho , Kita-ku , Okayama-shi, Okayama 700-8558, Japan), do hereby declare:

1. That I graduated from Tohoku University School of Medicine in May 1981 with an M.D. and Tohoku University Graduate School of Medicine in March 1987 with a Ph.D.

2. Work Experience

1988 -1990 Research Fellow at the Harvard Medical School (Boston, USA)

1989. August Assistant Professor of Department of Neurology at Tohoku Univ.

1995. August Lecturer of Department of Neurology at Tohoku Univ.

1996. March Associate Professor of Department of Neurology at Tohoku Univ.

1998. April Professor and Chairman of Neurology at Okayama Univ. Medical School

2002. April - 03.June Vice President of Okayama Univ. Hospital

Participating Societies

World Society of Cerebral Blood Flow & Metabolism (President 2009-2011, Chairman 2007)

World Society of Neurology, World Society of Stroke

International VAS-COG society, International Conference of Alzheimer's Disease

Japanese Society of Internal Medicine (Board of Trustee)

Japanese Society of Neurology (Executive Director, International Affair)

Japanese Society of Stroke (Executive Director, Chair International Committee)

Japanese Society of Cerebral Blood Flow & Metabolism (Executive Director, Chairman 2014)

Japanese Society of Dementia (Executive Director)

Japanese Society of VAS-COG (Executive Director, Secretary General)

Japanese Society of Clinical Genetics (Genetic Counselor)

Professional Organizations

2009-2011	President of World Society of CBF&M
2007	Chairman of 23'd International symposium of CBF&M (Osaka)
2006	Executive director of Japanese Society of Stroke
2003	Deputy Chief editor of Journal of CBF&M, finance committee of ISCBFM
2001	Executive director of Japanese Society of Neurology
2001-2005	Education committee member of International Society of CBFM
1997-2001	Director of International Society of CBFM
1991-1999	International Scientific Advisory Board of International Society of CBFM
1996	Advisory Committee Member of Japanese Society of Strokes
1996	Advisory Committee Member of Tohoku University
1994	Advisory Committee Member of Japanese Society of CBFM
1994	Advisory Committee Member of Japanese Society of Neurology

Sample Publications

Correlation of cerebral spinal fluid pH and HCO3(-) with disease progression in ALS.
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Clinical and pathological studies of familial amyotrophic lateral sclerosis (FALS) with SOD1 H46R mutation in large Japanese families.
Arisato T., Okubo R., Arata H., **Abe K.**, Fukada K., Sakoda S., Shimizu A., Qin X.H., Izumo S., Osame M., Nakagawa M.
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3. I have carefully reviewed the Office Action dated December 29, 2011 and reviewed the references cited therein. In particular, I have carefully reviewed Yoshino et al. (Neurological Therapeutics, 2003, Vol. 20, pp. 557-564). This reference is the primary reference used in all the remaining obviousness rejections.

It is my expert opinion and belief that Yoshino et al. fails to render obvious claims 1-40 either alone or in combination with the other cited references. In particular, it is my expert opinion and belief that the claimed methods improvement in the ALSFRS-R score is surprising and unexpected to a person of skill in the art for the below-noted reasons.

Amyotrophic lateral sclerosis (ALS) is an incurable disease. Unless a patient of ALS undergoes a tracheotomy and uses an artificial respirator, the patient will usually die within 2 to 5 years. At present, there is no therapy for completely curing ALS. Thus, maintaining the Quality of Life (QOL) of patients is the current therapy for ALS.

When the results of Yoshino et al. (Neurological therapeutics (2003) 20:557-564) are compared to the claimed invention, the ALSFRS-R score is improved by 0.6 points by use of the claimed invention. This ALSFRS-R score difference of 0.6 points arose in a half year. Thus, the ALSFRS-R score difference is 1.2 points in one year, 2.4 points in two years, and 6.0 points in five years.

It is my expert opinion and belief that these score differences between Yoshino and the claimed invention are surprising and unexpected to a person of skill in the art.

In Neurology 2005; 64:38-43 which was cited in the Declaration submitted November 22, 2011, it is mentioned that an ALSFRS-R score increase of 1.0 point increases the risk of death or tracheotomy by 7%. Thus, in the method of the claimed invention, the risk of death or tracheotomy is decreased by about 16% in two years, and by about 42% in five years, as compared with the case of Yoshino et al.

It is my expert opinion and belief that this decrease in risk of death or tracheotomy of the claimed invention in view of Yoshino et al. is surprising and unexpected to a person of skill in the art.

As mentioned above, most ALS patients will die or must undergo a tracheotomy within 2 to 5 years. According to the present invention, this risk of death or tracheotomy within 2 to 5 years can be reduced by 16-42%. In other words, the number of the patients who die or undergo a tracheotomy within 5 years after the onset of ALS can be decreased by 42% by use of the claimed invention over use of the invention in Yoshino et al. This effect has a great significance to the ALS patients, and is an unexpected advantageous effect.

Further, attached herewith is an article from the Journal of the Neurological Sciences, 169, 1999, pp. 13-21. This journal shows the breakdown for the ALSFRS-R score. The score corresponds to 12 different categories which are each ranked from 0-4. It is noted that over the course of a year, the claimed method suppresses a reduction in ALSFRS-R score by 1.2 points.

Examining the scale as detailed in the attached reference, it is noted that a reduction in 1 point can commonly result in a drastic reduction in the patient's quality of life, for instance, from being able to eat almost unassisted to requiring someone to cut up his or her food, or from intermittent use of a breathing assistance device to continuous use of a breathing assistance device during night, or alternatively, from use of such device at night to use of such device 24 hours a day. Thus, Applicants respectfully note that 0.6 points in half a year has a tremendously significant affect on an ALS patients' quality of life.

It is my expert opinion and belief that the improvement in the patients' quality of life by using the claimed invention in view of Yoshino et al. is surprising and unexpected. Thus, it is my expert opinion and belief that Yoshino et al. either alone or in view of the other cited references fail to render the claimed invention obvious as such references fail to teach or suggest the surprising and unexpected advantages of the claimed invention.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: March 19, 2012

Koji Abe

(Signature of Declarant)

PTO 11-4931

Japanese Article
Yoshino, et al.

Clinical Trials for Amyotropic Lateral Sclerosis with Free Radical Scavenger Edaravone
[Kin'ishukusei Sokusaku Kōkashō (ALS)ni-taisuru edaravone-o Mochiita Rinshō Shiken*]

Hiide Yoshino, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. July 2011

Translated by: FLS, Inc.

Translated Title:	CLINICAL TRIALS FOR AMYOTROPHIC LATERAL SCLEROSIS WITH FREE RADICAL SCAVENGER EDARAVONE
Japanese Title:	KIN'ISHUKUSEI SOKUSAKU KOKASHO (ALS)NI-TAISURU EDARAVONE O MOCHIITA RINSHO SHIKEN
Authors:	YOSHINO, HIIDE**; KIMURA, AKIO**, ***
Authors' Affiliation	**Department of Neurology, Kohnodai Hospital, National Center of Neurology and Psychiatry ***Department of Neurology and Geriatrics, Hospital of the University of Gifu
Source:	JAPANESE JOURNAL OF NEUROTHERAPY
Volume:	Vol. 20. No. 5 (2003), Pp. 557-584

Key Words: amyotrophic lateral sclerosis (ALS), edaravone, clinical trial, free radical, nitrotyrosine

Amyotrophic lateral sclerosis (ALS) is an intractable disease of the nerves wherein the motor nerve cells of the cerebrum, brain stem, and spinal cord is damaged and is fatal approximately three years after onset. Riluzole, which is a glutamic acid antagonist and the only drug approved for treatment of ALS, was effective in prolonging life for 3 to 6 months in two placebo control studies carried out in the United States and Europe[1,2]. However, the effect is mild and unfortunately was not effective in phase III trials carried out in Japan[3]. ALS drug therapy is still far from satisfactory and a useful therapeutic drug must be developed as soon as possible.

In recent years, research on elucidating the pathology of ALS has been progressing at an amazing speed. The greatest progress made thus far is most likely the elucidation of the pathology mechanism through oxidative stress which started with the discovery[4] of familial SOD-1 gene mutation. Despite the fact that the oxygen activity which eliminates the superoxide is normal, abnormal SOD-1 protein is thought to scavenge new functions and to cause motor nerve cell death[5]. This assumes toxicity[4] caused by formation of aggregates,

* Numbers in the margin indicate pagination in the foreign text.

hydroxyl radicals[7], peroxynitrite[8], and other toxicities caused by free radicals.

One known marker for oxidative stress is 3-nitrocyrocin. 3NT is characteristic in that peroxynitrite [$ONOO^-$], which is a radical, consists of molecules that bond with tyrosine. This 3NT increases in the spinal cords of transgenic ALS mice[5] and in autopsies of spinal cords of familial ALS patients accompanying SOD-1 gene mutations and spontaneous ALS (SALS) and even in the spinal cords of patients with sporadic ALS[20]. Deposition has been confirmed by immunological staining in the motor neurons[12,13]. Tohgi, et al., have also reported that 3NT increases in the SALS cerebrospinal fluid[13]. Based on these, oxidative stress caused by peroxynitrite is thought to play a great role in sporadic ALS which accounts for most cases of ALS. As a result, there are expectations for a therapeutic agent having the action of eliminating first and foremost peroxynitrite by protecting against damage to the motor neurons occurring in ALS.

Edaravone, a free radical scavenger that was approved as a therapeutic agent for acute phase cerebral infarction in April 2001, is thought to eliminate peroxide lipids as well as hydroxyl radicals (OH^-) which manifest in cerebral ischemia and to protect the neurons[14]. It has been reported that it has a suppressing effect /558 on the functional impedance in patients with acute phase cerebral infarction[15].

The author believes that edaravone may be effective even for ALS at sites where oxidative stress contributes due to radicals and is currently carrying out clinical trials where this drug is being administered to ALS patients.

1) open clinical trials

2) long-term open administration trials (phase II trials)

3) short-term placebo control double blind comparative trials

Of these, 1) and 3) are autonomous research carried out with the authorization of the Kohnodai Regional Ethics Committee; 2) consists of trials carried out at the request of Mitsubishi Well Pharma. Here we are focusing on the results of clinical trials in 1).

I. Open Administration Trials

We contacted the Kohnodai Regional Ethics Committee for approval of the trials in July 2001 and were authorized in November 2001.

1. Patients

Since these were initially exploratory trials involving administration of the drug to patients, we focused on patients with a variety of impairments so that we could see effects over a wide range. This means that although we excluded patients with respiratory distress and impairment of swallowing, we included patients who were on respirators or patients whose general state had stabilized due to nutrition via feeding with a tube.

2. Test Design

We carried out open trials by administering 30 mg of edaravone once per day for 14 days by an intravenous drip. When no diagnosis had been confirmed, no observation period was set and we carried out respiratory function tests and arterial blood gas analysis. Six months after the drug was administered, we carried out respiratory rehabilitation and administered the drug at the patient's expense for those patients wishing it and focused on evaluating the effectiveness in all of the cases by the intent-to-treat principle no matter what the intervention treatment.

Furthermore, since there were limitations on research expenses which affected the number of cases that could be studied, we initially set up 10 cases. However, as many patients wished to have the drug administered even after the number of cases had been at 10 and as there were no problems with safety, once the number of cases exceeded 10, we had the patients pay for the expenses themselves and administered the drug. As a result, since many patients wanted to continue with the drug, we continued to administer the drug for 10 days based on the long-term open administration trials (investigation).

3. Evaluation Categories

The effectiveness in the main evaluation categories was seen in terms of changes in the revised ALS functional rating scale (ALSFRS-R), respiratory function, and arterial blood gas for 6 months after the drug was administered. The ALSFRS-R was compared with changes

prior to administering the drug. Safety was studied by studying the general physical findings as well as blood and urine tests one week and two weeks after the drug was administered.

ALSFRS-R is a function evaluation measure of ALS created to develop an ALS therapeutic agent[16]. The Japanese language version of the ALSFRS-R has been validated between groups making the evaluations as well as inside the groups making the evaluations. It is understood that a stable effect can be obtained even if the evaluation is made by physicians or nurses[17].

When death occurred from respiratory insufficiency and when there had been a tracheotomy or the patient was on a respirator or when the patient was receiving assisted respiration using BiPAP for at least half a day or longer, we considered this to have reached the hard end point and the evaluation of the validity using ALSFRS-R was completed.

Secondary evaluation categories were cerebrospinal fluid protein made before administration of this drug was started and after administration of the drug was completed and the amount of 3-nitrotyrosine (3NT) in the cerebrospinal fluid. The 3NT was measured using the competitive enzyme immunoassay (EIA) method.

4. Results Thus Far

At the end of June 2003, there were 23 patients who did not have respiratory difficulty when the drug was first administered, who were not on a respirator, who did not reach a hard end point 6 months

after administration of the drug had started. The ALSFRS-R 6 months before the drug was administered to these patients was an average of 38.2 points; however, this had declined by 6.9 points to 31.3 points when the drug was first administered. The ALSFRS-R 6 months after administration of the drug was started for these 23 cases had declined 5.2 points to an average of 26.1 points (Figure 1).

Meanwhile, 12 cases reached the hard end point within 6 months after the drug was first administered. The ALSFRS-R 6 months before administration of the drug started in these 12 cases was an average of 36.6 points. However, it declined 15.6 points in 6 months and the average was 21.0 points when administration of the drug was first started. This was a patient group with rapid progress of the disease. When the drug was first administered, the patients were virtually bedridden and required almost total intervention in their daily lives.

Seven patients had come to hospital from a distance and it was not possible to observe their progress.

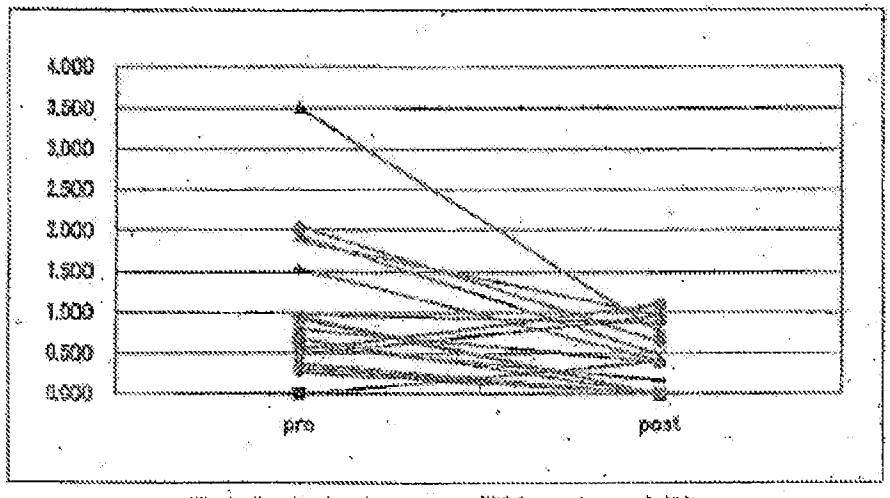

Fig. 1 Decreased 3-nitrotyrosine in CSF from patients with ALS
CSF 3-nitrotyrosine level was decreased significantly from 0.71ng/ml to 0.39ng/ml (N=11; p<0.007, paired T-test) after 14 days administration of edaravone.

Table 1 Safety profile of edaravone for serum liver enzymes, blood urea nitrogen (BUN), creatin, and creatin kinase (CK)

	pre-administration	post-14day administration	changes between pre- and post-administration
GOT (N = 70)	25.8 ± 11.7	24.4 ± 6.6	−1.4 ± 10.8
GPT (N = 70)	31.4 ± 26.1	26.8 ± 14.6	−4.7 ± 21.7
γ-GTP (N = 69)	35.8 ± 37.0	35.4 ± 34.3	−0.7 ± 28.7
BUN (N = 68)	9.1 ± 3.8	9.0 ± 3.9	−0.3 ± 3.2
Creatin (N = 69)	0.595 ± 0.18	0.584 ± 0.18	−0.01 ± 0.07
CK (61)	180 ± 133.4	152 ± 121.7	−24.8 ± 72.8

Regarding safety concerns for the drug metabolism, since there were cases in which this drug was subjected to gluconate conjugation and the renal function, liver function, and the CK are frequently high in ALS due to secretion from the kidneys, we observed the effect on the CK value. In evaluating the safety of the drug, we gathered a wide range of information including data on the drug administration period in the short-term placebo control double bind trials. No

tendency toward worsening was confirmed for the test values after administration compared to before the drug was administered in the blood, biochemical, and general urine tests among the safety evaluation categories. When this drug is administered, due caution must be exercised as acute renal failure has been confirmed as a grave adverse event. However, there was virtually no change in the value for BUN and creatinin compared to before the drug was administered. The liver enzymes in GOT, GPT, γ-GTP, and CK tended to decline after the drug was administered (Table 1).

In the secondary evaluation categories, the 3NT in the cerebrospinal fluid was an average of 0.71 ng/ml before the drug was administered; however, it was 0.29 ng/ml after the drug was administered which was a significant drop (N=25, p=0.007, paired t-test, Figure 2).

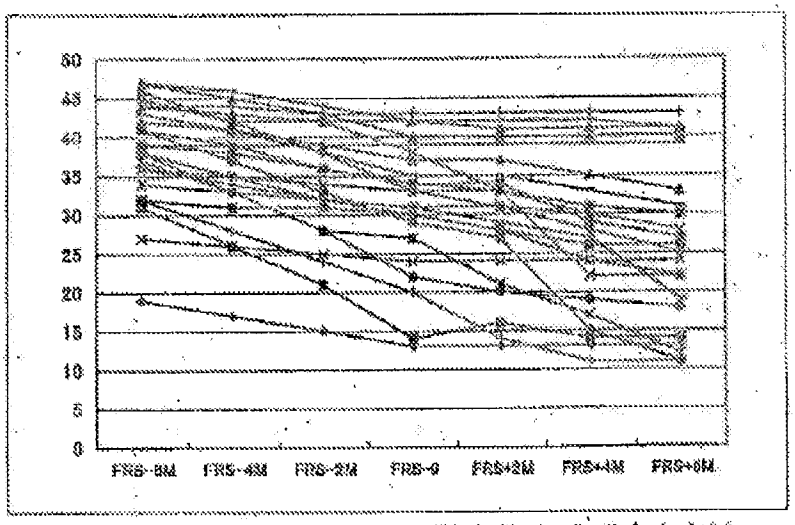

Fig. 8 Change of ALSFRS-R score in 22 cases with ALS who did not reach to the hard endpoint
At 3 month prior to the administration of edaravone, mean score was 38.2 and it reduced to be 31.3, resulting 6.9 point reduction. At 6 month after the administration of edaravone, mean ALSFRS-R score was 35.1, resulting 3.2 point reduction. Note that patients who started edaravone whose score showed more than 40, are not used to decrease the score.

Since the 3NT in the cerebrospinal fluid, which is the oxidative stress marker, significantly declined when edaravone was administered for 14 days, it could be expected that this will have an effect on the oxidative stress clinically and pharmacologically.

As a result, in considering the effectiveness of the drug, although many patients continued to receive the drug for 10 days each month on a long term basis, results were such that the decline in the ALSFRS-R was 6.9 for 6 months prior to administering the drug; however, there was a tendency toward a mild inhibition of 5.2. Meanwhile, in cases where the progress of the functional impairment was rapid, the effect on suppressing the progress was not clear.

From a safety aspect, there were no problematic side effects first and foremost such as renal insufficiency for which caution had been advised in patients with acute cerebral infarction within the scope of the ALS patients.

Based on the above, we believe that repeated administration of the drug to patients with ALS is safe and it is reasonable to carry out clinical trials on validating the short-term effect of the drug as well as the long-term effect.

II Short-term Placebo Control Double Blind Comparative Trials

Application to carry out these trials was made in April 2002 with the Ethics Committee and was approved in November 2002.

A single drug administration period during the open clinical trials was short term and consisted of 14 days. However, many patients wished to continue receiving the drug and an improvement in subjective symptoms was confirmed in some cases. Based on this, placebo control comparative trials were carried out including any changes in subjective symptoms as to whether there was an effect in short-term administration of the drug or if there was, for which symptoms it was effective.

1. Patients in Trials

The point of difference in the open trials was that patients who had undergone a tracheotomy were excluded even if they were on a respirator and their condition had stabilized. Even if the patient had generally stabilized, there was little advantage in going from /561

a comfortable home convalescence to being an in-patient in tests which could involve a placebo and it was difficult to make an objective determination as to the points when evaluating the efficacy so that these patients were excluded.

2. Test Design

We administered 30 mg/day of the edaravone or the placebo (saline solution) for 20 days Monday through Friday. We administered the drug only on weekdays to carry out the following operations to maintain the blind nature of the study. The preparation of the study drug was contracted to a nurse from the investigational drug control laboratory due to the importance of the double blind trials. The nurses dissolved 30 mg (20 ml) of the edaravone or the placebo (20 ml of saline solution) in 100 ml of saline solution in accordance with computerized random assignment and labeled them. When the study drug was prepared, other persons cooperating in the trials labeled it with the patient's name corresponding to the administration number. They were classed as outpatients or were moved to a hospital ward and other nurses and physicians administered the drug in drip form at the respective locations. It was not possible to know whether the patient had been administered the actual drug or the placebo by the physician or nurse.

We administered the actual drug (30 mg/day of edaravone) to all of the patients for 14 days after the double blind tests had been completed and the drug was withheld from the patients for 2 weeks so

that the patients participating in the placebo control trials could profit from this.

There were 40 target cases. The basis for setting these was to set a certain number of cases so that it would be possible to show that the 3NT in the cerebrospinal fluid declined significantly relative to the placebo group.

3. Evaluation Categories

The validity of the main evaluation categories covered ALSFRS-R, the Japanese language version of the Norris evaluation measure, muscle cramps, changes in pain, changes in the 3NT value in the cerebrospinal fluid, changes in respiratory function, and changes in arterial blood gas. A secondary evaluation category was changes in the 3NT in the cerebrospinal fluid. We studied exploratory oxidative stress and changes in the amount of manifestation of leucocyte messenger RNA related to cell death and decided to study the relation to the effect of the investigational drug. Based on the results of the open trials, this suggests that there are patients for whom the drug is effective (responders) and patients for whom the drug is thought not to be effective (non-responders). As a result, we set out to study whether these could be determined on the m-RHA level.

We studied the clinical symptoms and blood and urine tests for the drug safety on the 10th and 20th days of administration.

4. Progress Made Thus Far

We started the first case in November 2002. Registration of the 40 cases was completed up to July 31, 2003, and double blind tests were completed up to case 38. We intend to complete the remaining two cases in September including the actual drug administration period. Thus far, there have been no cases of problematic side-effects throughout the test period.

III Observations

Ever since SOD-1 gene abnormalities were found in FALS[4], it was found that oxidative stress plays a great role in the pathology of ALS and a drug which has anti-oxidant action can be expected to be effective against ALS. However, thus far, none of the drugs such as N-acetylcystein[12], selegilin[19], vitamin E[20], glutathione and other drugs having an anti-oxidant action used in the clinical trials for ALS have proven to be effective. Meanwhile, edaravone has the action of eliminating the free radicals starting with, first and foremost, peroxynitrite, which is thought to be related to the progress of the disease in ALS so that an effect can be expected compared to preexisting anti-oxidant drugs. It has also been reported that not only is 3NT wherein peroxynitrite bonds to tyrosine an oxidative stress marker but a Parkinson model is also created by injecting this substance into the striate body[21], impairment occurs in the skeleton of cultivated endothelial cells[23], and the fact that 3NT declined due to administration of the edaravone itself is reason to expect that it has a motor neuron protection action.

In the open trials results reported here, we provided data on ALSFRS-R as a validity evaluation. When we studied the patient groups that did not reach the hard end point with 6 months of administration of the drug, there was a decline in the score of 6.9 in the 6-month period prior to administration of the drug whereas the score 6 months after administration of the drug declined 5.2 points. Based on this, it was possible to expect that the progress of the ALS could be inhibited by repeated administration of a daily 30 mg dose of edaravone for 10 days. We can assume that the peroxynitrite, hydroxyl radicals, peroxide lipids and other free radicals play a great role in the pathology of the disease. On the other hand, there was a marked decline in ALSFRS-R and the effect of /562 the drug was not clear in the group of patients where progress of the disease was quick. We believe that this may be a factor, other than the radicals, causing the cell death of many motor neurons which contributes to the pathology.

The ALSFRS-R score is said to decline linearly[18]. However, there were several cases where the progress was by no means linear, which progressed rapidly from that point and then the progress slowed down. In patients where the disease progresses at an average speed, the fact that a progress-inhibiting effect is suggested must take into consideration the fact that this is ex-post facto analysis from which the patient group with the rapidly progressing disease was excluded. Furthermore, in this study edaravone was administered and symptomatic

treatment was carried out, which suggests that there is a certain degree of validity, first and foremost, for respiratory rehabilitation. In general, there is little evidence for effective rehabilitation for ALS[26]; however, participating in clinical trials and rehabilitation is motivation in tackling the disease proactively by the patient and we believe that it is possible to inhibit worsening of the functional prognosis[25]. In any case, rehabilitation must be implemented to validate the effect of the drug and once the design is accepted on its ethicality so that there is sufficient merit for the subjects participating and even for the placebo control group, the validity of this drug must be validated by long-term placebo control comparative trials.

Sufficient study is also required for administration of the drug 10 days per month at a daily dose of 30 mg. The cell tissue in the penumbra region is thought to be protected by eliminating the peroxide lipids and other radicals from the infarction nidus in cerebral infarction and the effect of the drug is thought to appear clinically. However, since we believe that ALS involves not the cell membrane but rather that damage to the mitochondrial membrane[24] is related to the pathology, the drug must be able to reach the inside of the cell membrane. As a result, a single dose that is greater than that administered for cerebral infarction may be the one for which we can expect an effect in ALS.

The drug administration period and the frequency of the dose must be studied. Although the site where radical production, first and foremost, of the peroxynitrite is not clear in ALS, it is possible that there may be microglia which surround the motor neurons[27] and the production of radicals is thought to be continuous. Taking this into consideration, the frequency and period of once per day, 10 days per month, may not be sufficient.

The period in which administration of the drug is started must also be studied. Although the reason why ALS is a progressive disease is not well understood, there are results of in vitro studies in which the peroxynitrite changed the properties of the spinal cord astrocytes and caused motor neuron death[26]. If this is the case, administering this drug at the initial phase of the disease when peroxynitrite is eliminated early would make it possible to expect greater clinical validity. It can be assumed from Figure 1 that the group having an ALSFRS of 40 or more points which did not require intervention in daily life tended to have a smaller decline in the score 6 months later.

Based on the abovementioned circumstances, a plan must be drawn up for a long-term placebo control double blind comparative study of validation tests including the benefits to the subjects, the ethical concerns, and a realistic appraisal of carrying it out.

Although edaravone can be expected to be used as an ALS therapeutic drug, based on the results of the open trials, it is

impossible to completely inhibit the progress of ALS using this drug alone. Although this drug has a radical elimination action, the mitochondrial cells which produce the radicals are thought to send out signals which induce cell death first and foremost of the TNF-α and damage the motor neurons[33]. We assume that in the future, study will be carried out not only on eliminating radicals for treatment of ALS, combined administration of a drug which inhibits the mitochondria function which provides the signals which induce cell death is more effective. Thus far it has been from this point of view that cerecoxib[30] which is a cycloxygenase-2 inhibitor and minocyclin[31] and the like have been reported to be effective in vitro or in transgenic ALS mice. Furthermore, the effectiveness has still not been demonstrated clinically; however, combined use of nerve protein factors and the like will most likely be an issue requiring further study.

[Notes]

(generic name)	(commercial name)
Edaravone	Radicut
Acetylcysteine	aceteine
selegiline hydrochloride	FP
vitamin E	Yubel
glutathione	Tation
celecoxib	celebrex (not approved in Japan)
minocyclin	minocyclin

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